TRS
TOXICOLOGY/REGULATORY SERVICES, INC.

201-15017

December 31, 2003

Mr. Mike Leavitt, Administrator
US Environmental Protection Agency
PO Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know Program, AR-201

Re: Test Plans for CAS RNs 54395-52-7 and 38103-06-9

Toxicology/Regulatory Services (TRS) is submitting two Test Plans/Robust Summaries on behalf of General Electric Company – Plastics (GE Plastics; Registration Number 1100342). Please add the attached Test Plans and Robust Summaries for 1H-Isoindole-1,3(2H)-dione, 5,5'-[(1-methylethylidene)bis(4,1-phenyleneoxy)]bis[2-methyl- (Bisphenol A Bisimide; CAS RN 54395-52-7) and 1,3-Isobenzofurandione, 5,5'-[(1-methylethylidene)bis(4,1-phenyleneoxy)]bis-(Bisphenol A Dianhydride; CAS RN 38103-06-9) sponsored by GE Plastics to the list of those chemicals to begin testing in 2003. Please address any comments to:

Dr. Ronald Joiner
Manager, Global Toxicology
General Electric Company
One Plastics Avenue
Pittsfield, MA 01201
Phone: 413-448-6323; Fax: 866-607-2387
EMAIL: Ronald.Joiner@GEP.GE.COM

Thank you,

John P. Van Miller Digitally signed by John P. Van Miller
DN: CN = John P. Van Miller, C = US, O = TRS
Date: 2003.12.31 08:24:48 -05'00'

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201-15017A

U.S. HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM

ROBUST SUMMARY

1,3-Isobenzofurandione, 5,5'-[(1-methylethylidene) bis(4,1-phenyleneoxy)]bis-
(Bisphenol A Dianhydride; CAS RN 38103-06-9)

Prepared by:
General Electric Company
Pittsfield, MA, USA

Prepared for:
U.S. Environmental Protection Agency
Washington, D.C., USA

December 31, 2003

CHEMICAL IDENTITY AND USE INFORMATION

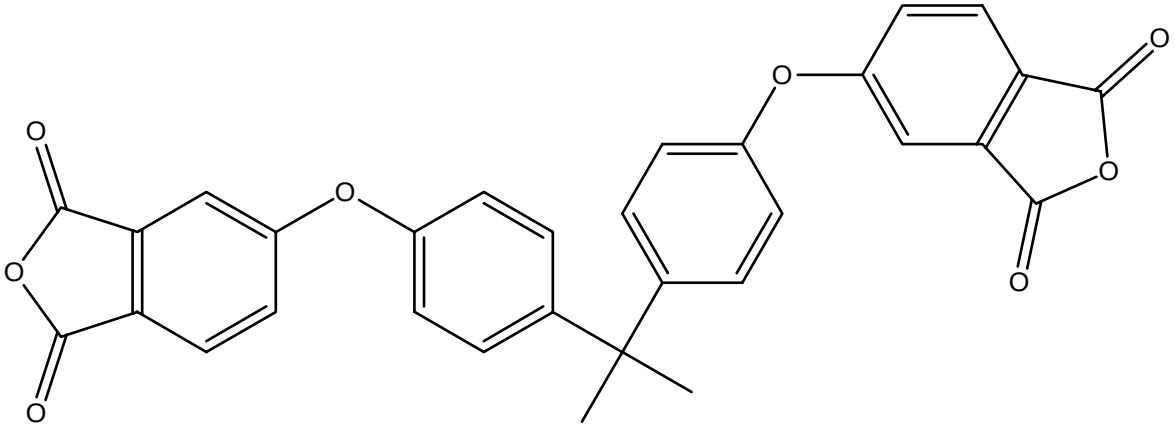
CAS RN

38103-06-9

CHEMICAL NAME

1,3-Isobenzofurandione, 5,5'-[(1-methylethylidene)bis(4,1-phenyleneoxy)]bis-
(hereafter called Bisphenol A Dianhydride)

STRUCTURE, MOLECULAR FORMULA, MOLECULAR WEIGHT



Molecular Formula: $C_{31}H_{20}O_8$
Molecular Wt.: 520.49

OTHER CHEMICAL IDENTITY INFORMATION

Bisphenol A Dianhydride
4,4′-((Isopropylidene)bis(p-phenyleneoxy))diphthalic dianhydride
2,2-bis(4-(3,4-dicarboxyphenoxy)phenyl)propanedianhydride
BPA-DA
Bisphenol-A diphthalic anhydride
Biphenol Dianhydride

PURITY

Typical purity of 4,4'-BPA-DA is 97 wt%. Mono N-methylimide of BPA-DA comprise approximately 2 wt% yielding a purity of all isomers > 98 wt%.

USE PATTERN

BPA-DA is a chemical intermediate that is primarily used as a reactive intermediate to make high molecular weight polyetherimide polymers.

TEST PLAN

Bisphenol A Dianhydride **CAS RN: 38103-06-9**		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL AND CHEMICAL DATA								
1.0	Melting Point	N	N	N	N	N	N	Y
2.0	Boiling Point	N	N	N	N	N	N	Y
3.0	Vapor Pressure	N	N	N	N	N	N	Y
4.0	Partition Coefficient	N	N	N	N	N	N	Y
5.0	Water Solubility	N	N	N	N	N	N	Y
ENVIRONMENTAL FATE AND PATHWAY								
6.0	Photodegradation	N	N	N	N	N	N	Y
7.0	Stability in Water	N	N	N	N	N	N	Y
8.0	Transport and Distribution	N	N	N	N	N	N	Y
9.0	Biodegradation	N	N	N	N	N	N	Y
ECOTOXICITY								
10.0	Acute Toxicity to Fish	N	N	N	N	N	N	Y
11.0	Toxicity to Algae	N	N	N	N	N	N	Y
12.0	Acute Toxicity to Daphnia	N	N	N	N	N	N	Y
TOXICITY								
13.0	Acute Toxicity	Y	N	N	Y	N	Y	N
14.0	Genotoxicity *In Vitro or In Vivo* (Chromosome Aberration Tests)	N	N	N	N	N	N	Y
15.1	Genotoxicity *In Vitro* (Bacterial Test)	Y	N	Y	Y	N	Y	N
15.2	Genotoxicity *In Vitro* (Mammalian Cells)	Y	Y	Y	N	N	Y	N
16.0	Repeated Dose Toxicity	Y	N	Y	Y	N	Y	N
17.0	Reproductive Toxicity	N	N	N	N	N	N	Y
18.0	Developmental Toxicity / Teratogenicity	Y	N	Y	Y	N	Y	N

ROBUST SUMMARY

201-15017B

PHYSICAL AND CHEMICAL DATA

1.0 MELTING POINT

No data were found. Study according to OECD Guideline 102 in progress.

2.0 BOILING POINT

No data were found. Study according to OECD Guideline 103 in progress.

3.0 VAPOR PRESSURE

No data were found. The calculated vapor pressure of BPA-DA was less than the detection limit of the most sensitive (gas saturation) method. Therefore, in lieu of conducting a study according to OECD Guideline 104, an Expert Statement will be prepared describing the scientific rationale for not determining the vapor pressure.

4.0 PARTITION COEFFICIENT ($Log_{10}P_{ow}$)

No data were found. Study according to OECD Guideline 107 in progress.

5.0 WATER SOLUBILITY

5.1 SOLUBILITY

No data were found. Study according to OECD Guideline 105 in progress.

5.2 pH VALUE, pKa VALUE

No studies were found.

ENVIRONMENTAL FATE AND PATHWAYS

6.0 PHOTODEGRADATION

When physical/chemical properties testing is complete, the resulting data will be coupled with modeling efforts to predict the environmental fate and pathways of Bisphenol A Dianhydride.

7.0 STABILITY IN WATER

No data were found. Study according to OECD Guideline 111 in progress.

8.0 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS, INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

8.1 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

When physical/chemical properties testing is complete, the resulting data will be coupled with modeling efforts to predict the environmental fate and pathways of Bisphenol A Dianhydride.

Results:	All rats survived and gained weight during the 14-day post-dosing period. There were no signs of toxicity during the 14-day post-dosing observation period and there were no remarkable gross pathologic lesions found at necropsy.
Reference:	Myers, R. C. (1988) Unpublished report for Project No. 50-667 entitled "Biphenol Dianhydride Acute Toxicity and Primary Irritancy Studies" dated January 19, 1988 for General Electric Company, Pittsfield, MA, USA; from Bushy Run Research Center, Export, PA, USA.
Reliability:	(Klimisch Code 1) Valid without restrictions – Guideline study.

13.1.2

Type:	LD_0 [ ] LD_{100} [ ] LD_{50} [ ] LD_{L0} [ ] Other [X]
Species/Strain:	Rat/Spartan (albino)
Sex:	Male
# Animals:	4
Vehicle:	Corn oil
Value:	Not applicable
Method:	Not specified
GLP:	Yes [ ] No [X] ? [ ]
Test Substance:	AR No. 82896 (Bisphenol A Dianhydride; BPA-DA; CAS RN 38103-06-9); from General Electric Company; Purity: See "Chemical Identity and Use Information" section.
Remarks:	Rats weighed from 220 to 234 grams at the initiation of the study. Animals were fasted from food overnight prior to dosing. The test material was administered to two rats each at doses of 500 and 5000 mg/kg. The test compound was suspended in corn oil at concentrations enabling the administration of 10 ml/kg at the 500 mg/kg dose and 20 ml/kg at the 5000 mg/kg dose. All rats were observed for mortality for a period of 14 days. Body weights were measured initially and at 14 days.
Results:	All rats survived the 14-day observation period and exhibited normal body weight gains.
Reference:	Wazeter, F. X. and E. I. Goldenthal (1974) Unpublished report for Project No. 313-035 entitled "Acute Toxicity Screening Studies in Rats and Rabbits" dated May 16, 1974 for General Electric Company, from International Research and Development Corporation, Mattawan, MI, USA.
Reliability:	(Klimisch Code 2) Valid with restrictions. Only two animals dosed, one per dosage group.

13.2 ACUTE INHALATION TOXICITY

No studies were found.

13.3 ACUTE DERMAL TOXICITY

13.3.1

Type:	LD_0 [ ] LD_{100} [ ] LD_{50} [X] LD_{L0} [ ] Other [ ]
Species/Strain:	Rabbit/New Zealand White
Value:	> 2000 mg/kg
Method:	US EPA Toxic Substance Control Act (TSCA) Health Effects Test Guidelines (1982 and 1984)
GLP:	Yes [ ] No [X] ? [ ]

Test Substance:	Biphenol Dianhydride (Bisphenol A Dianhydride; BPA-DA; CAS RN 38103-06-9); from General Electric Company; Purity: > 99%.
Remarks:	Ten rabbits (5/sex), weighing 2.0 to 3.0 kg and approximately 12 to 18 weeks of age, were dosed with a single dermal application of 2000 mg biphenol dianhhydride/kg body weight for 24 hours. The test substance was moistened with distilled water and applied to the dorsal surface of the clipped trunk of each rabbit. The coverage was approximately 43 mg of sample per cm^2 of rabbit skin surface. A double layer of gauze sheeting was wrapped around the trunk and secured with adhesive tape. Polyethylene sheeting and bandaging tape were then wrapped around the trunk. Animals were returned to their cages. After 24 hours, all covering was removed and as much excess test material as possible was carefully removed. Treated rabbits were observed frequently for signs of toxic effects on the first day of the test and twice daily thereafter for 14 days.
Results:	All rabbits survived and there were no signs of toxicity during the test. All rabbits gained weight during the 14-day post-application period. No local skin reactions were apparent. Gross pathologic evaluation revealed only a pitted surface of the kidneys of one male.
Reference:	Myers, R. C. (1988) Unpublished report for Project No. 50-667 entitled "Biphenol Dianhydride Acute Toxicity and Primary Irritancy Studies" dated January 19, 1988 for General Electric Company, Pittsfield, MA, USA; from Bushy Run Research Center, Export, PA, USA.
Reliability:	(Klimisch Code 1) Valid without restrictions. Guideline study.

13.3.2

Type:	LD_0 [ ] LD_{100} [ ] LD_{50} [ ] LD_{L0} [ ] Other [X]
Species/Strain:	Rabbit/New Zealand White
Value:	Not applicable
Method:	Not specified
GLP:	Yes [ ] No [X] ? [ ]
Test Substance:	AR No. 82896 (Bisphenol A Dianhydride; BPA-DA; CAS RN 38103-06-9); from General Electric Company; Purity: See "Chemical Identity and Use Information" section.
Remarks:	Two New Zealand White rabbits (one male and one female) were used at each of two doses. The rabbits weighed from 2413 to 2729 grams at study initiation. Body weights were measured initially and at 14 days. The compound was applied to the clipped back of each rabbit. Two rabbits received 200 mg of the test substance/kg body weight and two rabbits received 2000 mg of the test substance/kg body weight. The application area was wrapped with a gauze bandage and occluded with plastic wrap. After 24 hours, the bandages were removed and the application areas were washed with tepid tap water. The rabbits were observed for mortality for a period of 14 days.
Results:	All rabbits survived the 14 day observation period. Three of the rabbits exhibited body weight gains and one rabbit showed a slight (81 gram) loss in body weight during the 14-day observation period.
Reference:	Wazeter, F. X. and E. I. Goldenthal (1974) Unpublished report for Project No. 313-035 entitled "Acute Toxicity Screening Studies in Rats and Rabbits" dated May 16, 1974 for General Electric Company, from International Research and Development Corporation, Mattawan, MI, USA.

Reliability: (Klimisch Code 2) Valid with restrictions. Only two rabbits exposed per dose.

14.0 GENETIC TOXICITY *IN VITRO* OR *IN VIVO* (CHROMOSOMAL ABERRATIONS)

No studies were found. Study according to OECD Guideline 473 in progress.

15.0 GENETIC TOXICITY *IN VITRO*

15.1 BACTERIAL TEST

15.1.1

Type:	Bacterial reverse mutation assay (Ames test)
System of testing:	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538
Concentrations:	0, 0.3, 1.0, 3.0, 10 and 30 mg/plate
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:	Negative
Cytotoxicity conc.:	With metabolic activation: 30 mg/plate in TA1537 and TA1538 only Without metabolic activation: ≥ 10 mg/plate
Precipitation conc.:	Observed in the cytotoxicity test only at 50 mg/plate
Genotoxic effects:	With metabolic activation: positive [ ]; ambiguous [ ]; Negative [X] Without metabolic activation: positive [ ]; ambiguous [ ]; Negative [X]
Method:	Description of test procedure: The *Salmonella typhimurium* strains were supplied by Dr. Bruce N. Ames, University of California, Berkeley, USA. A preliminary cytotoxicity test was conducted with 10 dose levels of the test substance ranging from 0.01 to 50 mg/plate to determine the doses for the mutagenicity assay. No cytotoxicity was evident; however, the highest dose (50 mg/plate) produced a dense precipitate which precluded the ability to count colonies. For the mutagenicity assay, 100 µl of the appropriate solvent, control or test chemical solution was added to a sterile tube containing 2 ml of top agar and a 100 µl aliquot of the appropriate bacterial culture. Either 0.5 ml of S9 mix or 0.5 ml of phosphate-buffered saline was added for tests with or without metabolic activation, respectively. The top agar mixture was then poured onto a Vogel-Bonner Medium E agar plate. Each dose was tested in triplicate with all five bacterial strains. The plates were transferred to a darkened 37°C incubator after hardening and incubated for 48-72 hours. Bacterial colonies were counted manually or by an automatic counter. An examination of the background lawn was also recorded. *Solvent and Positive controls*: The test substance was suspended in dimethylsulfoxide (DMSO), which also was used as the solvent control. For the nonactivation assay, the following positive control substances were used: 4-nitro-o-phenylenediamine (0.01 mg/plate for strains TA98 and TA1538); sodium azide (0.01 mg/plate for strains TA100 and TA1535); and 9-aminoacridine (0.06 mg/plate for strain 1537). 2-Aminoanthracene (2.5 µg/plate) was used as the positive control substance for the activation assay in all strains. Criteria for evaluating results: The spontaneous reversion for the solvent controls should be within the laboratories historical range. The positive controls should demonstrate that the test systems are

responsive with known mutagens. A test chemical is considered to be a bacterial mutagen if the number of revertant colonies is at least twice the solvent control for at least one dose and there is evidence of a dose-related increase in the number of revertant colonies.

Activation system: S9 liver homogenate prepared from Aroclor 1254-induced Sprague-Dawley male rats. The S9 mix was prepared fresh each day of testing.

Year: 1988.

GLP: Yes [X] No [ ] ? [ ]

Test substance: Biphenol Dianhydride (Bisphenol A Dianhydride; BPA-DA; CAS RN 38103-06-9); from General Electric Company; Purity: > 99%.

Results: The number of revertants/plate produced by treatment of the bacteria with the test substance at all concentrations and in all tester strains was reported to be less than or approximately equal to the number of revertants in the vehicle-treated negative control group, with and without metabolic activation. The test material was therefore concluded to not be mutagenic in this assay.

Mean Number of Revertants Per Plate
Activation: None

Dose (mg/plate)	TA98	TA100	TA1535	TA1537	TA1538
Solvent (DMSO)	18	94	19	7	7
0.3	20	72	13	6	9
1.0	17	70	11	2 (t)	3 (t)
3.0	21	77	10	4	6
10	17	55 (s)	6 (s/t)	5	3 (s/t)
30	19	49 (s)	12 (t)	4 (t)	6 (s)
Positive Control	928	1847	1740	208	1130

t = Toxic: Clearing of background lawn, or average number of colonies < ½ solvent control value.
s = Sparse growth of background lawn; counts not included in calculation of mean.

Mean Number of Revertants Per Plate
Activation: Rat Liver S9

Dose (mg/plate)	TA98	TA100	TA1535	TA1537	TA1538
Solvent (DMSO)	30	95	9	6	21
0.3	21	84	11	4	16
1.0	30	82	9	6	15
3.0	25	77	10	5	17
10	19	76	9	1 (s/t)	10 (t)
30	20	77	7	3	10 (t)
Positive Control	2372	1910	83	125	1164

t = Toxic: Clearing of background lawn, or average number of colonies < ½ solvent control value.
s = Sparse growth of background lawn; counts not included in calculation of mean.

Conclusion: The test substance did not exhibit mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions according to the evaluation criteria.

Reference: Guzzie, P. J. and E. R. Morabit (1988) Unpublished report for Project No. 51-511 entitled "Biphenol Dianhydride

	Salmonella/Microsome (Ames) Bacterial Mutagenicity Assay" dated February 17, 1988 for General Electric Company, Pittsfield, MA, USA; from Bushy Run Research Center, Export, PA, USA.
Reliability:	(Klimisch Code 2) Valid with restrictions. Similar to guideline study; confirmatory assay not performed.
15.1.2	
Type:	Bacterial reverse mutation assay
System of testing:	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538
Concentrations:	0, 1, 10, 100, 500, 1000, 2500, 5000 and 10,000 μg/plate
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:	Negative
Cytotoxicity conc.:	5000 and 10,000 μg/plate in strains TA1537 and TA1538; and slightly toxic to strains TA1535 and TA100 at 5000 and 10000 μg/plate and to TA98 at 10,000 μg/plate.
Precipitation conc.:	None
Genotoxic effects:	With metabolic activation: positive [ ]; ambiguous [ ]; Negative [X] Without metabolic activation: positive [ ]; ambiguous [ ]; Negative [X]
Method:	Ames et al., Mutation Research 31:347, 1975 Description of test procedure: The plate test consisted of direct revertant colony counts obtained from a set of selective agar plates seeded with populations of mutant cells suspended in a semisolid overlay. Approximately 0.1 to 0.2 ml of the test organisms were treated with the test substance in the presence and absence of a metabolic activation system (Aroclor 1254-treated rat liver supernatant). One plate was used per concentration. The plates were incubated for approximately 48 hours at 37 ºC, and scored for the number of colonies growing on each plate. *Solvent and Positive controls:* Dimethylsulfoxide (DMSO) was the solvent for the test substance and served as the solvent control (at 100 μl/plate). For the non-activation assay, the following positive control substances were used: sodium azide (for strains TA1535 and TA100); 2-Nitrofluorene (for strains TA1538 and TA98); and 9-aminoacridine (for strain TA1537). The positive control substance, 2-anthramine, was used for all tester strains in the presence of metabolic activation. Criteria for evaluating results: The solvent control values must be within the normal historical control range and the presence of a dose response is required for establishing mutagenicity. For strains TA1535, TA1537 and TA1538, a test substance producing a positive response equal to three times the solvent control value is considered mutagenic. For strains TA98 and TA100, a test substance producing a positive response equal to twice the solvent control value is considered mutagenic. In addition, a positive response must be repeated in a separate assay. *Activation system*: S9 liver homogenate prepared from Aroclor 1254-induced Sprague-Dawley male rats. The S9 mix was prepared fresh each day of testing.

Year: 1981
GLP: Yes [X] No [ ] ? [ ]
Test substance: AR #93480 (Bisphenol A Dianhydride; BPA-DA; CAS RN 38103-06-9); from General Electric Company; Purity: See "Chemical Identity and Use Information" section.
Results: The number of revertants/plate produced by treatment of the bacteria with the test substance at all concentrations and in all tester strains, was reported to be less than or approximately equal to the number of revertants in the solvent-treated negative control group, with and without metabolic activation.

Revertants Per Plate
Activation: None

Dose (µg/plate)	TA1535	TA1537	TA1538	TA98	TA100
Solvent (DMSO)	18	8	10	52	118
Solvent (DMSO)	19	14	17	54	132
1.0	18	12	18	45	99
10	11	6	23	56	128
100	13	7	13	44	123
500	16	8	19	46	111
1000	11	5	17	57	116
2500	14	4	11	56	84
5000	3	0	0	35	43
10,000	1	0	0	4	8
Positive Control	584	190	820	876	1143
Positive Control	645	299	925	913	1249

Revertants Per Plate
Activation: Rat Liver S9

Dose (µg/plate)	TA1535	TA1537	TA1538	TA98	TA100
Solvent (DMSO)	15	9	21	68	137
Solvent (DMSO)	17	20	23	73	138
1.0	18	10	28	47	114
10	10	10	30	69	148
100	9	12	18	67	147
500	17	5	20	57	124
1000	18	12	20	65	134
2500	10	9	16	53	104
5000	9	2	4	54	86
10,000	3	0	0	18	42
Positive Control	443	227	1555	1510	1608
Positive Control	450	308	1756	1554	1661

Conclusion: The test substance did not exhibit mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions according to the evaluation criteria.

Reference: Jagannath, D. R. and D. J. Brusick (1981) Unpublished report for Project No. 20988 entitled "Mutagenicity Evaluation of 02-81-011535-016 AR #93480" dated April 1981 for General Electric, Schenectady, NY, USA; from Litton Bionetics, Inc., Kensington, MD, USA.

Reliability:	(Klimisch Code 2) Valid with restrictions. Acceptable study report that meets basic scientific principles.
15.1.3	
Type:	Bacterial reverse mutation assay (Ames test)
System of testing:	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538; *Saccharomyces cerevisiae* strain D4
Concentrations:	0, 0.1, 1.0, 10, 100 and 500 μg/plate
Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:	Negative
Cytotoxicity conc.:	With metabolic activation: not stated Without metabolic activation: not stated
Precipitation conc.:	None
Genotoxic effects:	With metabolic activation: positive [ ]; ambiguous [ ]; Negative [X] Without metabolic activation: positive [ ]; ambiguous [ ]; Negative [X]
Method:	Ames et al., Mutation Research 31:347, 1975 Description of test procedure: The plate test consisted of direct revertant colony counts obtained from a set of selective agar plates seeded with populations of mutant cells suspended in a semisolid overlay. Approximately 10^8 cells were treated with the test substance in the presence and absence of a metabolic activation system (Aroclor 1254-treated rat liver supernatant). One plate was used per concentration. The plates were incubated for 48 hours at 37 ºC, and scored for the number of colonies growing on each plate. *Solvent and Positive controls:* Dimethylsulfoxide (DMSO) was the solvent for the test substance and served as the solvent control. For the non-activation assay, the following positive control substances were used: Methylnitrosoguanidine (for strains TA1535, TA100 and D4); 2-Nitrofluorene (for strains TA1538 and TA98); and quinacrine mustard (for strain TA1537). The positive control substances, 2-anthramine (strains TA1535 and TA100), 2-acetylaminofluorene (strains TA1538 and TA98) and 8-aminoquinoline (strain TA1537) were used with metabolic activation. The positive control substance used for DA without activation was not identified in the report. Criteria for evaluating results: The solvent control values must be within the normal historical control range and the presence of a dose response is required for establishing mutagenicity. For strains TA1535, TA1537 and TA1538, if the solvent control value is within the normal range, a test substance producing a positive response over three concentrations with the lowest increase equal to twice the solvent control is considered mutagenic. For strains TA98, TA100 and D4, a test substance producing a positive response over three concentrations with the lowest increase equal to twice the solvent control (TA100) or two to three times the solvent control (TA98 and D4) is considered mutagenic. In addition, a positive response must be repeated in a separate assay. Activation system: S9 liver homogenate prepared from Aroclor 1254-induced male Sprague-Dawley rats.
Year:	1977

GLP: Yes [ ] No [X] ? [ ]

Test substance: 09-77-011154-026 (Bisphenol A Dianhydride; BPA-DA; CAS RN 38103-06-9); from General Electric Company; Purity: See "Chemical Identity and Use Information" section.

Results: The number of revertants/plate produced by treatment of the bacteria with the test substance at all concentrations and in all tester strains was reported to be less than or approximately equal to the number of revertants in the solvent-treated negative control group, with and without metabolic activation.

Revertants Per Plate
Activation: None

Dose (µg/plate)	TA1535	TA1537	TA1538	TA98	TA100	D4
Solvent (DMSO)	10	14	13	28	169	32
0.1	16	15	11	26	140	38
1.0	19	10	16	31	189	37
10	17	12	16	30	202	41
100	17	15	13	29	206	42
500	12	17	15	28	233	28
Positive Control	653	619	>1000	>1000	>1000	593

Revertants Per Plate
Activation: Rat Liver S9

Dose (µg/plate)	TA1535	TA1537	TA1538	TA98	TA100	D4
Solvent (DMSO)	17	13	24	35	267	23
0.1	10	18	16	31	196	21
1.0	17	12	24	34	238	10
10	17	14	29	26	217	23
100	11	17	20	38	254	28
500	9	10	13	32	245	25
Positive Control	131	213	574	891	831	48

Conclusion: The test substance did not exhibit mutagenic activity in any of the assays conducted in this evaluation and was considered not mutagenic under these test conditions according to the evaluation criteria.

Reference: Jagannath, D. R. and D. J. Brusick (1977) Unpublished report for Project No. 20838 entitled "Mutagenicity evaluation of 09-77-011154-026" dated October 1977 for General Electric, Schenectady, NY, USA; from Litton Bionetics, Inc., Kensington, MD, USA.

Reliability: (Klimisch Code 2) Valid with restrictions. Acceptable study report that meets basic scientific principles.

15.2 NON-BACTERIAL *IN VITRO* TEST (MAMMALIAN CELLS)

Type: *In vitro* mammalian cell gene mutation test (Mouse lymphoma assay)

System of testing: Mouse lymphoma L5178Y cells

Concentration: 0, 50, 75, 100, 125 and 150 µg/mL with activation
0, 25, 50, 75, 100 and 125 µg/mL without activation

Metabolic activation:	With [ ]; Without [ ]; With and Without [X]; No data [ ]
Results:	Negative with and without metabolic activation.
Cytotoxicity conc.:	With metabolic activation: 500 μg/mL Without metabolic activation: ≥ 150 μg/mL
Genotoxic effects:	+ ? - With metabolic activation: [ ] [ ] [X] Without metabolic activation: [ ] [ ] [X]
Method:	OECD Test Guideline 476 (1998)
GLP:	Yes [X] No [ ] ? [ ]
Test Substance:	Bisphenol A Dianhydride (BPA-DA; CAS RN 38103-06-9; from General Electric Plastics): Purity: 98.2%
Remarks:	Description of test procedure: The preliminary toxicity assay was used to establish the optimal dose levels for the mutagenesis assay. L5178Y cells were exposed to the solvent alone and nine concentrations of test article ranging from 0.05 to 500 μg/mL in both the absence and presence of S9-activation with a 4-hour exposure and without activation with a 24-hour exposure. Cell population density was determined 24 and 48 hours after the initial exposure to the test article. The cultures were adjusted to $3x10^5$ cells/mL after 24 hours only. Toxicity was measured as suspension growth of the treated cultures relative to the growth of the solvent control cultures after 48 hours. The mutagenesis assay was carried out by combining $6x10^6$ L5178Y/$TK^{+/-}$ cells, medium or S9 activation mixture and 100 μL dosing solution of test or control article in solvent or solvent alone and incubated for 4 (with and without activation) or 24 (without activation) hours. The positive controls were treated with MMS (at 15 and 20 μg/mL for the 4-hour exposure or 2.5 and 5.0 μg/mL for the 24-hour exposure) and 7,12-DMBA (5.0 and 7.5 μg/mL). Expression of the mutant phenotype: For expression of the mutant phenotype, the cultures were counted and adjusted to $3x10^5$ cells/mL at approximately 24 and 48 hours after treatment. Cultures with less than $3x10^5$ cells/mL were not adjusted. For expression of the $TK^{-/-}$ cells, two flasks per culture were cloned for TFT (trifluorothymidine, the selective agent) or VC (viable count). The cells were diluted in cloning medium to concentrations of $3x10^6$ cells/100/mL for the TFT flask and 600 cells/100mL for the VC flask. Cells were plated and incubated for 10-14 days. Scoring procedures: The VC plates were counted for the total number of colonies per plate and the total relative growth determined. The TFT-resistant colonies were counted for each culture with ≥ 20% total relative growth (including at least one concentration with ≥ 10% but ≤ 20% total growth). The diameters of the TFT-resistant colonies for the positive and solvent controls and, in the case of a positive response, the test article-treated cultures were determined over a range of approximately 0.2 to 1.1 mm. Evaluation of results: The cytotoxic effects of each treatment condition were expressed relative to the solvent-treated control for

suspension growth over two days post-treatment and for total growth (suspension growth corrected for plating efficiency at the time of selection). The mutant frequency (number of mutants per 10^6 surviving cells) was determined by dividing the average number of colonies in the three TFT plates by the average number of colonies in the three corresponding VC plates and multiplying by the dilution factor ($2x10^{-4}$) then multiplying by 10^6. In evaluation of the data, increases in mutant frequencies that occurred only at highly toxic concentrations (i.e., less than 10% total growth) were not considered biologically relevant. The following criteria are presented as a guide to interpretation of the data: (1) A result was considered positive if a concentration-related increase in mutant frequency was observed and one or more dose levels with 10% or greater total growth exhibited mutant frequencies of ≥ 100 mutants per 10^6 clonable cells over the background level, (2) A result was considered equivocal if the mutant frequency in treated cultures was between 55 and 99 mutants per 10^6 clonable cells over the background level, (3) A result was considered negative if the mutant frequency in treated cultures was fewer than 55 mutants per 10^6 clonable cells over the background level.

Criteria for a Valid Test: For the negative control, the spontaneous mutant frequency of the cultures must be within 20 to 120 TFT-resistant mutants per 10^6 surviving cells. The cloning efficiency of the solvent control group must be greater than 50%. For positive controls, at least one concentration of each positive control must exhibit mutant frequencies of ≥ 100 mutants per 10^6 clonable cells over the background level. The colony size distribution for the MMS positive control must show an increase in both small and large colonies. For the BPA-DA cultures, a minimum of four analyzable concentrations with mutant frequency data was required.

Activation system: Aroclor 1254-induced rat liver S9 was used as the metabolic activation system. The S9 was prepared from male Sprague-Dawley rats induced with a single intraperitoneal injection of Aroclor 1254, 500 mg/kg, five days prior to sacrifice.

Results:

The maximum dose tested in the preliminary toxicity assay was 500 μg/mL. Visible precipitate was present at ≥ 150 μg/mL in treatment medium. No visible precipitate was present at concentrations of ≤ 50 μg/mL in treatment medium. The osmolality of the solvent control was 442 mmol/kg and the osmolality of the highest soluble dose, 50 μg/mL, was 437 mmol/kg. Suspension growth relative to the solvent controls was 0% at 150 μg/mL without activation with 4- and 24-hour exposures and 7% at 500 μg/mL with S9 activation and 4-hour exposure. Based on the results of this preliminary test the concentrations selected for the mutagenesis assay were 0, 50, 75, 100, 125 and 150 μg/mL with activation and 0, 25, 50, 75, 100 and 125 μg/mL without activation.

Results for cultures treated for four hours (initial assay): Visible precipitate was present at 150 μg/mL. In the non-activated system, suspension growth ranged from 14 to 107%. In the activated system, suspension growth ranged from 103 to 115%. One cloned culture treated with 125 μg/mL without activation exhibited a mutant

frequency between 55 and 99 mutants per 10^6 clonable cells greater than the solvent control. The total growths ranged from 14 to 112% for the non-activated cultures at concentrations of 25 to 125 µg/mL and 108 to 146% for the S9-activated cultures at concentrations of 50 to 150 µg/mL. The results of the initial 4-hour exposure assay were negative in the absence and presence of S9 activation. Because no unique metabolic requirements were known about the test article, only an extended treatment assay was performed in the absence of S9 for a 24-hour exposure period.

Results for cultures treated for 24 hours (extended treatment assay):
Visible precipitate was present at 150 µg/mL. Cultures treated with concentrations of 25, 50, 75, 100 and 125 µg/mL were cloned and produced a range in suspension growth of 89 to 115%.

One cloned culture (treated with 125 µg/mL) exhibited a mutant frequency of between 55 and 99 mutants per 10^6 clonable cells over that of the solvent control. A dose-response trend was not observed. The total growths ranged from 98% to 133% at concentrations of 25 to 125 µg/mL.

The TFT-resistant colonies for the positive and solvent control cultures from both assays were sized according to diameter over a range from approximately 0.2 to 1.1 mm. The colony sizing for the MMS positive control yielded the expected increase in small colonies, verifying the adequacy of the methods used to detect small colony mutants.

Cloning Data for L5178Y/TK$^{+/-}$ Mouse Lymphoma Cells Treated with BPA-DA in the Absence of Exogenous Metabolic Activation Initial Assay (4-hour exposure)

Dose Level (µg/mL)	Replicate	TFT Colonies				VC Colonies				Mutant Freq.[a]	Induced Mutant Freq.[b]	% Total Growth[c]
		Counts			Mean	Counts			Mean			
0 (solvent)	1	94	90	92	92 ± 2	176	140	171	162 ± 16	113	--	--
0 (solvent)	2	34	22	+	28 ± 5	168	130	127	142 ± 19	40	--	--
Mean Solvent Mutant Frequency = 76												
25	A	84	67	17	56 ± 28	165	133	178	159 ± 19	71	-6	112
25	B	30	37	33	33 ± 3	151	169	164	161 ± 8	41	-35	109
50	A	112	103	50	88 ± 27	176	175	189	180 ± 6	98	22	110
50	B	38	68	52	53 ± 12	185	151	186	174 ± 16	61	-16	106
75	A	83	58	21	54 ± 25	155	150	162	156 ± 5	69	-7	18
75	B	65	70	28	54 ± 19	152	129	131	137 ± 10	79	3	22
100	A	77	67	73	72 ± 4	165	153	150	156 ± 6	93	16	18
100	B	79	76	68	74 ± 5	151	171	165	162 ± 8	92	15	15
125	A	63	79	78	73 ± 7	158	162	164	161 ± 2	91	14	19
125	B	94	76	86	85 ± 7	105	122	122	116 ± 8	147	70	14
Positive Control - Methyl Methanesulfonate (µg/mL)												
15	--	104	83	+	94 ± 9	77	103	93	91 ± 11	205	129	39
20	--	212	155	129	165 ± 35	71	48	66	62 ± 10	536	460	22

Solvent = DMSO

+ = Culture lost

[a] Mutant frequency (per 10^6 surviving cells) = (Average # TFT colonies / average # VC colonies) x 200

[b] Induced mutant frequency (per 10^6 surviving cells) = mutant frequency - average mutant frequency of solvent controls

[c] % Total growth = (% suspension growth x % cloning growth) / 100

Cloning Data for L5178Y/TK$^{+/-}$ Mouse Lymphoma Cells Treated with BPA-DA in the Presence of Exogenous Metabolic Activation Initial Assay (4-hour exposure)

Dose Level (µg/mL)	Replicate	TFT Colonies				VC Colonies				Mutant Freq.[a]	Induced Mutant Freq.[b]	% Total Growth[c]
		Counts			Mean	Counts			Mean			
0 (solvent)	1	59	68	35	54 ± 14	212	101	65	126 ± 63	86	--	--
0 (solvent)	2	80	17	89	62 ± 32	80	212	232	175 ± 67	71	--	--
Mean Solvent Mutant Frequency = 78												
50	A	73	63	55	64 ± 7	169	152	199	173 ± 19	73	-5	130
50	B	50	13	64	42 ± 22	181	194	191	189 ± 6	45	-33	141
75	A	71	60	81	71 ± 9	146	168	162	159 ± 9	89	11	121
75	B	72	86	84	81 ± 6	195	159	166	173 ± 16	93	15	130
100	A	96	85	93	91 ± 5	215	198	158	190 ± 24	96	18	146
100	B	94	78	81	84 ± 7	195	190	156	180 ± 17	94	15	138
125	A	101	78	70	83 ± 13	177	196	202	192 ± 11	87	8	133
125	B	101	87	90	93 ± 6	162	177	96	145 ± 35	128	49	108
150*	A	89	94	79	87 ± 6	177	194	179	183 ± 8	95	17	125
150*	B	85	80	57	74 ± 12	178	157	182	172 ± 11	86	8	122
Positive Control - 7,12 Dimethylbenz(a)anthracene (µg/mL)												
2.5	--	198	51	60	103 ± 67	54	50	80	61 ± 13	336	258	35
4	--	238	269	275	261 ± 16	99	59	50	69 ± 21	752	674	14

Solvent = DMSO

***** Precipitating concentration

[a] Mutant frequency (per 10^6 surviving cells) = (Average # TFT colonies / average # VC colonies) x 200

[b] Induced mutant frequency (per 10^6 surviving cells) = mutant frequency - average mutant frequency of solvent controls

[c] % Total growth = (% suspension growth x % cloning growth) / 100

Cloning Data for L5178Y/TK$^{+/-}$ Mouse Lymphoma Cells Treated with BPA-DA in the Absence of Exogenous Metabolic Activation Extended Treatment Assay (24-hour exposure)

Dose Level (µg/mL)	Replicate	TFT Colonies				VC Colonies				Mutant Freq.[a]	Induced Mutant Freq.[b]	% Total Growth[c]
		Counts			Mean	Counts			Mean			
0 (solvent)	1	60	32	57	50 ± 13	158	160	143	154 ± 8	65	--	--
0 (solvent)	2	24	30	37	30 ± 5	120	131	127	126 ± 5	48	--	--
Mean Solvent Mutant Frequency = 56												
25	A	72	32	39	48 ± 17	171	140	160	157 ± 13	61	4	100
25	B	39	40	40	40 ± 0	158	146	137	147 ± 9	54	-2	98
50	A	47	54	24	42 ± 13	175	165	162	167 ± 6	50	-7	113
50	B	117	86	40	81 ± 32	131	160	155	149 ± 13	109	53	108
75	A	40	45	33	39 ± 5	183	130	143	152 ± 23	52	-5	114
75	B	32	24	32	29 ± 4	136	164	198	166 ± 25	35	-21	133
100	A	104	109	46	86 ± 29	190	145	142	159 ± 22	109	52	111
100	B	66	78	78	74 ± 6	137	163	197	166 ± 25	89	33	127
125	A	87	41	94	74 ± 24	176	169	117	154 ± 26	96	40	113
125	B	72	74	86	77 ± 6	122	119	168	136 ± 22	113	57	113
Positive Control - Methyl Methanesulfonate (µg/mL)												
5	--	163	136	132	144 ± 14	66	76	86	76 ± 8	378	322	40
7.5	--	214	156	140	170 ± 32	70	72	85	76 ± 7	449	393	32

Solvent = DMSO

[a] Mutant frequency (per 10^6 surviving cells) = (Average # TFT colonies / average # VC colonies) x 200

[b] Induced mutant frequency (per 10^6 surviving cells) = mutant frequency - average mutant frequency of solvent controls

[c] % Total growth = (% suspension growth x % cloning growth) / 100

Conclusions: All criteria for a valid study were met as described in the protocol. The results of the L5178Y/TK$^{+/-}$ Mouse Lymphoma Mutagenesis Assay indicate that, under the conditions of this study, the mutagenicity of BPA-DA was concluded to be negative without activation with 4- and 24-hour exposures and negative with S9 activation with a 4-hour exposure.

Reference: San, R.H.C. and J.J. Clarke (2003) Unpublished report no AA64EY.704.BTL entitled "*In vitro* mammalian cell gene mutation test (L5178Y/TK$^{+/-}$ mouse lymphoma assay)" DRAFT dated December 3, 2003 for General Electric Company, Pittsfield, MA, USA; from BioReliance Corp., Rockville, MD, USA.

Reliability: (Klimisch Code 1) Valid without restrictions.

16.0 REPEATED DOSE TOXICITY

16.1

Species/Strain:	Rat/Sprague-Dawley Crl:COBS®, CD®, (SD) Br
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No data [ ]
Route of Administration:	Oral, Dietary feed
Exposure Period:	30 days
Frequency of Treatment:	Daily
Post Exposure Observation Period:	None
Dose:	0, 1, 2, and 4% of BPA-DA in basal diet (approximately 646 – 765, 1277 – 1490, and 2750 – 3160 mg/kg/day, respectively)
Control Group:	Yes [X] No [ ] No data [ ] Concurrent no treatment [X] Concurrent vehicle [ ] Historical [ ]
NOAEL:	4% (approximately 2750 to 3160 mg/kg/day)
LOAEL:	> 4%
Method:	Groups of 10 rats/sex were fed BPA-DA at concentrations of 0, 1, 2 and 4% in the diet. All rats were observed for mortality twice each day. Clinical signs and body weights were recorded at initiation and weekly thereafter. Food consumption was recorded weekly. After 31 days of treatment, all surviving rats were weighed, killed and a gross necropsy was performed. At necropsy, the liver and kidneys of each animal were weighed and organ to body weight ratios determined. The following tissues were preserved from all animals: brain, pituitary, thoracic spinal cord, eyes, salivary glands, thyroid, parathyroids, thymus, trachea, esophagus, lung, heart, liver, spleen, kidneys, adrenals, stomach, pancreas, duodenum, jejunum, ileum, colon, cecum, mesenteric lymph node, urinary bladder, testes with epididymides and prostate (males), ovaries and uterus (females), femur, costal bone marrow, skeletal muscle, and all gross lesions. Microscopic evaluation was conducted on sections of the lungs, liver, brain and kidneys from rats of all treatment groups. Reproductive organs were not evaluated histologically. The following statistical tests were utilized to evaluate body weight changes, total food consumption and organ weights: Bartlett's test for homogeneity of variance and one-way classification analysis of variance (ANOVA). Since the ANOVA proved to be not significant for all of the analyses, no other tests were performed. All analyses were performed at the 5% one-tailed probability level.
Year:	1982
GLP:	Yes [X] No [ ] ? [ ]
Test Substance:	Bisphenol A Dianhydride (BPA-DA; CAS RN 38103-06-9); Lot UI-82-4 from General Electric Company; Purity: See "Chemical Identity and Use Information" section.
Results:	No deaths occurred during the study. No compound-related clinical observations were noted throughout the study. Body weight and food consumption data of the compound-treated males and females were generally comparable to those of their respective controls. Individual and mean terminal body weights, absolute organ weights and organ weights relative to terminal body weight were not affected by treatment. No compound-related organ or tissue changes were evident macroscopically or microscopically.

Reference:	Burdock, G. A. and W. Kundzins (1982) Unpublished report number 349-262 entitled "Thirty-Day Subchronic Oral Toxicity Study in Rats, BPA-BI and BPA-DA" dated December 17, 1982 for General Electric Company, Mount Vernon Indiana, USA; from Hazleton Laboratories America, Inc., Vienna, VA, USA; and Burdock, G. A. (1984) Unpublished addendum to final report number 349-262 entitled "Thirty-Day Subchronic Oral Toxicity Study in Rats, BPA-BI and BPA-DA" dated December 22, 1984 for General Electric Company, Mount Vernon Indiana, USA; from Hazleton Laboratories America, Inc., Vienna, VA, USA.
Reliability:	(Klimisch Code 2) Valid with restrictions. Minimal data collected for a repeat dose study.

17.0 REPRODUCTIVE TOXICITY

No studies were found. Study according to OECD Guideline 421 in progress.

18.0 DEVELOPMENTAL TOXICITY/TERATOGENICITY

18.1

Species/Strain:	Rabbit, New Zealand White
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration:	Oral (gavage)
Duration of Test:	29 days
Exposure Period:	Days 6 through 18 of gestation
Frequency of Treatment:	Daily
Dose:	1000 mg/kg/day
Control group:	Yes [X] No [ ] No data [ ] Concurrent no treatment [ ] Concurrent vehicle [X] Historical [ ] Positive Control (thalidomide)
NOEL Maternal Toxicity:	Not established (based on decrease in body weight gain)
NOEL Teratogenicity:	> 1000 mg/kg/day
GLP:	Yes [X] No [ ] ? [ ]
Test Substance:	Bisphenol A Dianhydride (BPA-DA; CAS RN 38103-06-9); Lot UI-82-4 from General Electric Company; Purity: See "Chemical Identity and Use Information" section.
Method:	Ninety mature New Zealand White female rabbits were obtained from Dutchland Laboratory Animals, Inc., Denver, PA for use in this study. The animals were acclimated for a minimum of 22 days prior to the initiation of the study. During the period of acclimation, the rabbits were examined for general health and appearance. The animals were uniquely identified by ear tag and provided commercial rabbit ration (Purina lab Rabbit Chow®) and tap water *ad libitum*. The environment of the study room was maintained at 70-78 ºC, relative humidity of 53-86% and a 12-hour light/dark cycle. At Day 0 of gestation, the body weights ranged from 2845 to 4700 grams. The animals were artificially inseminated with sperm from the laboratory breeding stock five hours after induction of ovulation with chorionic gonadotropin. Five groups were included in this study; for the purposes of this summary, only three groups (control, positive control, and BPA-DA treated) will be discussed. Sixteen animals per group (to obtain at least 12 pregnant) were treated with vehicle (0.5%

carboxymethyl cellulose), positive control (thalidomide; 150 mg/kg/day) or BPA-DA (1000 mg/kg/day). Thalidomide and BPA-DA were suspended in vehicle to provide dose volumes of 1.5 and 2.5 ml/kg, respectively. Control dose volume was 4.0 ml/kg. The dose was administered from gestation day (gd) 6 through 18, approximately the same time each day, and was based on each individual body weight on gd 6 (starting on gd 11, two animals in the control group, four animals in the thalidomide group and three animals in the BPA-DA group were dosed based on gd 11 body weight). All of the animals were observed daily for mortality, moribundity and clinical signs. Body weights were recorded on gd 0, 6, 11, 15, 19 and 29. Individual food consumption was recorded weekly. On gd 29, the animals were sacrificed, examined for gross pathology of the external surface and viscera, and the uterus excised and weighed. The fetuses were taken by cesarean section and the following recorded for each litter: the number of corpora lutea per ovary; the number and placement of uterine implantation sites; live and dead fetuses; early and late resorptions; and any other abnormalities. Fetuses were removed from the placenta, individually identified, examined externally, weighed and measured from the frontal-parietal suture to the base of the tail (crown-rump distance). Cesarean sections were also performed on dams that were found dead, sacrificed moribund or sacrificed due to early delivery. The number of corpora lutea, implantations, resorptions and live or dead fetuses was recorded.

Visceral Examination of Fetuses: The unfixed fetuses underwent visceral examination according to the method of Staples. All of the fetuses were opened by longitudinal incision, the sex determined and examined grossly both externally and internally. Major organs were inspected *in situ* with special attention to the heart and major blood vessels. The heads of approximately one-third of the fetuses were removed, fixed in Bouin's solution, sectioned by Wilson's freehand sectioning technique for examination of the eyes, palate, nasal septum and brain. The prepared sections were then re-examined against a light box with the aid of magnification.

Skeletal Examination of Fetuses: Following visceral examination, all fetuses (minus the head for approximately one-third of the fetuses) were eviscerated and placed in 95% ethyl alcohol. After fixation and dehydration, the skeletons were stained in a potassium hydroxide-alizarin red solution. The skull, vertebral column, rib cage, pectoral and pelvic girdles, long bones and extremities of each skeleton were examined for degree of ossification, bone alignment, and possible anomalies. Examinations were performed with the aid of magnification on a light box.

Statistical Analyses: Mean maternal body weight changes, food consumption, percentage data (implantations, resorptions and males), and fetal viability were analyzed in the following order: Levene's test for homogeneity of variance; if the variances proved to be homogeneous, the data were analyzed by one-way classification analysis of variance (ANOVA); if the variance proved to be heterogeneous, a series of transformations was performed until homogeneity was achieved followed by ANOVA. If ANOVA was significant, the Games and Howell modification of the Tukey-Kramer honestly significant difference test was used to compare groups.

Pregnancy rates were analyzed by Fisher's exact test. External, visceral, and skeletal anomalies were evaluated by a multiple proportions test. Analysis of covariance (ANCOVA) was used to analyze mean fetal weights and lengths with the litter used as the experimental unit. Levene's test and ANOVA were evaluated at the 5% one-tailed probability level. Control vs. treatment group mean comparisons were evaluated at the 5% two-tailed probability level.

Range-finding study: A range-finding study was conducted to select the dose used in this study. Four non-pregnant New Zealand White rabbits were dosed with BPA-DA at 2000 mg/kg/day for the first six days and, following a three-day rest period, the dose was changed to 1000 mg/kg/day for the remaining seven days of the study. Compound-related clinical signs included depression, slight depression, anorexia, soft feces, ataxia and compound-colored urine stains in the pan. Two of the four rabbits died; one on Day 12 and the other on Day 16. Based on this study, 1000 mg/kg/day was selected for the teratology study.

Results: Weight loss was observed in the thalidomide- and BPA-DA-treated groups during the treatment period. Statistical evaluation of body weight change did not, however, reveal any significant differences between treated and control groups. No effects on food consumption or gross pathology of the dams were observed. The following tables summarize the fetal results:

Summary of Mean Ovarian, Uterine, and Litter Data

Parameter	Control (Vehicle)	Thalidomide (Positive Control)	BPA-DA (1000 mg/kg/day)
Number of dams	16	16	16
Number pregnant	14	16	13
Pregnancy rate (%)	88	100	81
Number dams surviving to gd 29 (survival rate)	13 (93%)	15* (100%)	12 (92%)
Mean number of			
Corpora lutea	13.4	12.2	11.4
Implantations	9.4	8.3	6.5
Resorptions-total	1.2	5.3	2.1
Fetuses – live	7.5	3.4	4.5
– dead	0.5	0	0.1
Indices (mean per litter)			
Implantation efficiency (%)	73.6	68.1	57.0
Incidence of resorption (%)	17.2	61.0	31.0
Incidence of fetal mortality (%)	3.8	0	0.9
Incidence of fetal viability (%)	79.2	39.1	68.1
Live fetuses			
Mean body weight (g) – males	40.91	38.36	42.80
– females	39.90	37.60	41.78
Mean length (cm) – males	9.49	9.03	9.42
– females	9.33	8.92	9.39
Percent Males	51.5	58.0	47.1
Mean uterine weights – gravid (g)	485.3	228.3	315.4

* One animal died accidentally on gd 8

Summary of Mean Incidence of Abnormal Fetuses per Litter

Parameter	Control (Vehicle)	Thalidomide (Positive Control)	BPA-DA (1000 mg/kg/day)
External			
# of litters examined	12	11	9
# of litters with anomalous fetuses	2	10*	3
% of litters with anomalous fetuses	16.7	90.9	33.3
Mean values (per litter)			
# of fetuses with variants	0	0.5	0
Incidence of variants (%)	0	14.4	0
# of fetuses with anomalies	0.3	2.7	0.6
Incidence of anomalies (%)	2.4	64.1	8.2
Visceral – Fetal Heads			
# of litters examined	12	9	8
# of litters with anomalous fetuses	0	3	0
% of litters with anomalous fetuses	0	33.3	0
Mean values (per litter)			
# of fetuses with variants	0	0.1	0
Incidence of variants (%)	0	3.7	0
# of fetuses with anomalies	0	0.4	0
Incidence of anomalies (%)	0	16.7	0
Visceral – Torso and Limbs			
# of litters examined	12	11	9
# of litters with anomalous fetuses	0	8*	1
% of litters with anomalous fetuses	0	72.7	11.1
Mean values (per litter)			
# of fetuses with variants	0.8	2.9	0.4
Incidence of variants (%)	11.1	63.9	8.7
# of fetuses with anomalies	0	1.5	0.1
Incidence of anomalies (%)	0	38.8	1.6
Skeletal – Skulls			
# of litters examined	12	11	9
# of litters with anomalous fetuses	0	2	0
% of litters with anomalous fetuses	0	18.2	0
Mean values (per litter)			
# of fetuses with variants	0.5	1.6	1.2
Incidence of variants (%)	11.3	60.9	33.7
# of fetuses with anomalies	0	0.2	0
Incidence of anomalies (%)	0	11.4	0
Skeletal – Torso and Limbs			
# of litters examined	12	11	9
# of litters with anomalous fetuses	0	10*	1
% of litters with anomalous fetuses	0	90.9	11.1
Mean values (per litter)			
# of fetuses with variants	0.6	3.9	0.8
Incidence of variants (%)	6.9	91.7	16.4
# of fetuses with anomalies	0	2.2	0.1
Incidence of anomalies (%)	0	54.4	1.2

* Statistically significantly different from vehicle control group ($p < 0.05$)

Conclusion:	There were no differences from control in the thalidomide or BPA-DA dose groups for maternal, ovarian or uterine data. The thalidomide-treated group exhibited changes consistent with the known teratogenic effect of this compound. The thalidomide group may additionally have had an increase in resorptions and exhibited a possible fetotoxic effect as demonstrated by slightly decreased mean body weights and lengths of the fetuses. There were no effects on any fetal parameters from BPA-DA treatment. Based on the results of this study, BPA-DA is not a developmental toxin.
Reference:	Burdock, G. A. (1983) Unpublished report number 349-267 entitled "Teratogenicity Study in Rabbits, PI BPA-BI, BPA-DA" dated August 25, 1983 for General Electric Company, Pittsfield, MA, USA; from Hazleton Laboratories America, Inc., Vienna, VA, USA.
Reliability:	(Klimisch Code 1) Reliable without restrictions.

18.2

Species/Strain:	Rat; Crl:CD®(SD)BR
Sex:	Female [X]; Male [ ]; Male/Female [ ]; No data [ ]
Route of Administration:	Oral (gavage)
Duration of Test:	20 days
Exposure Period:	Days 6 through 15 of gestation
Frequency of Treatment:	Daily
Dose:	1000 mg/kg/day
Control group:	Yes [X] No [ ] No data [ ] Concurrent no treatment [ ] Concurrent vehicle [X] Historical [ ]
NOEL Maternal Toxicity:	None – based on decrease maternal weight gain
NOEL Teratogenicity:	> 1000 mg/kg/day
GLP:	Yes [X] No [ ] ? [ ]
Test Substance:	Bisphenol A Dianhydride (BPA-DA; CAS RN 38103-06-9); from General Electric Company; Purity: See "Chemical Identity and Use Information" section.
Method:	One hundred twenty, successfully mated Sprague-Dawley female rats, obtained from Charles River Breeding Laboratories, Inc., (Portage, MI), were used in this study. Prior to in-house breeding, the rats were examined for general health and appearance. The animals were uniquely identified by ear tag and provided commercial rat ration (Purina Certified Rodent Chow®) and tap water *ad libitum*. The environment of the study room was monitored daily and a 12-hour light/dark cycle was used. Animals were mated one male to one female for 17 days. The day that vaginal sperm or a copulation plug was observed was designated Day 0 of gestation. At Day 0 of gestation, the body weights ranged from 200 to 289 grams. Six groups were included in this study; for the purposes of this summary, only two groups (control, and BPA-DA-treated) will be discussed. Twenty-four animals per group were treated with vehicle (0.5% carboxymethyl cellulose) or BPA-DA (1000 mg/kg/day). Dose volume was 10.0 ml/kg. The dose was administered from gestation day (gd) 6 through 15, approximately the same time each day, and was based on the most recently recorded body weight. All of the animals were observed daily for mortality, moribundity and clinical signs. Body weights and food consumption were recorded on gd 0, 6,

8, 12, 16 and 20. On gd 20, the animals were sacrificed, examined for gross pathology of the external surface and viscera, and the uterus excised and weighed. The fetuses were taken by cesarean section and the following recorded for each litter: the number of corpora lutea per ovary; the number and placement of uterine implantation sites; live and dead fetuses; early and late resorptions; and any other abnormalities. Fetuses were removed from the placenta, individually identified, examined externally, and weighed.
Visceral Examination of Fetuses: Approximately one-third of the live fetuses were selected for visceral examination according to the method of Wilson.
Skeletal Examination of Fetuses: The remaining fetuses were eviscerated and placed in 95% ethyl alcohol. After fixation and dehydration, the skeletons were stained in a potassium hydroxide-alizarin red solution. The skull, vertebral column, rib cage, pectoral and pelvic girdles, long bones and extremities of each skeleton were examined for degree of ossification, bone alignment, and possible anomalies.
Statistical Analyses: Mean maternal body weight changes, food consumption, percentage data (implantations, resorptions and males), and fetal viability were analyzed in the following order: Levene's test for homogeneity of variance; if the variances proved to be homogeneous, the data were analyzed by one-way classification analysis of variance (ANOVA); if the variance proved to be heterogeneous, a series of transformations was performed until homogeneity was achieved followed by ANOVA. If ANOVA was significant, the Dunnett's test was used to compare groups. Pregnancy rates, clinical observations and fetal skeletal observations were analyzed by Cochran-Armitage and Fisher-Irwin Exact Tests. Analysis of covariance (ANCOVA) was used to analyze mean fetal weights with the litter used as the experimental unit. Levene's test and ANOVA were evaluated at the 5% one-tailed probability level. Control vs. treatment group mean comparisons were evaluated at the 5% two-tailed probability level.

Range-finding study: A range-finding study was conducted to select the dose used in this study. Five pregnant Sprague-Dawley rats were dosed with BPA-DA at doses of 150, 400 or 1000 mg/kg/day from days 6 through 15 of gestation. A slight decrease in maternal body weight gain was observed at 1000 mg/kg/day. No fetal effects were observed at any dose. Based on this study, 1000 mg/kg/day was selected for the teratology study.

Results: Mean body weight was significantly lower than the control group on gd 8, 12, 16 and 20 and mean weight gain was significantly lower than control for gd 6-16. Mean maternal food consumption was significantly lower than control for gd 6-8 and 8-12. No effects on gross pathology of the dams were observed. The following tables summarize the fetal results:

Summary of Mean Ovarian, Uterine, and Litter Data

Parameter	Control (Vehicle)	BPA-DA (1000 mg/kg/day)
Number of dams	24	24
Number pregnant	23	24
Pregnancy rate (%)	96	100
Number dams surviving to gd 29 (survival rate)	24 (100%)	24 (100%)
Mean number of		
Corpora lutea	16.9	15.9
Implantations (% Efficiency)	14.8 (89)	14.3 (90)
Resorptions-total	0.9	0.4
Fetuses – live	14.0	13.8
– dead	0	0
Live fetuses		
Mean body weight (g) – males	3.6	3.5
– females	3.3	3.4
Mean uterine weights – gravid (g)	76.3	75.2

Summary of Mean Incidence of Abnormal Fetuses per Litter

Parameter	Control (Vehicle)	BPA-DA (1000 mg/kg/day)
External Variations		
Litter Incidence	23	24
# of litters examined	3	3
# of litters with anomalous fetuses	13	13
% of litters with anomalous fetuses		
Fetal Incidence	4	4
# of fetuses with variants	1.2	1.2
Incidence of variant (%)		
External Malformations		
Litter Incidence	23	24
# of litters examined	1	0
# of litters with anomalous fetuses	4.3	0
% of litters with anomalous fetuses		
Fetal Incidence	1	0
# of fetuses with variants	0.3	0
Incidence of variant (%)		
Soft Tissue Variations		
Litter Incidence	23	24
# of litters examined	6	6
# of litters with anomalous fetuses	26	25
% of litters with anomalous fetuses		
Fetal Incidence	9	9
# of fetuses with variants	9.2	8.8
Incidence of variant (%)		
Soft Tissue Malformations		
Litter Incidence	23	24
# of litters examined	0	0
# of litters with anomalous fetuses	0	0
% of litters with anomalous fetuses		
Fetal Incidence	0	0
# of fetuses with variants	0	0
Incidence of variant (%)		
Skeletal Variations		
Litter Incidence	23	24
# of litters examined	23	23
# of litters with anomalous fetuses	100	96
% of litters with anomalous fetuses		
Fetal Incidence	120	120
# of fetuses with variants	54	52
Incidence of variant (%)		

Summary of Mean Incidence of Abnormal Fetuses per Litter

Parameter	Control (Vehicle)	BPA-DA (1000 mg/kg/day)
Skeletal Malformations		
Litter Incidence	23	24
# of litters examined	1	0
# of litters with anomalous fetuses	4.3	0
% of litters with anomalous fetuses		
Fetal Incidence	1	0
# of fetuses with variants	0.4	0
Incidence of variant (%)		

Conclusion: Mean body weight and weight gain were reduced for BPA-DA treated dams in this study. There were no differences from control in the BPA-DA dose groups for ovarian or uterine data. There were no treatment-related effects on any fetal parameters from BPA-DA treatment. Based on the results of this study, BPA-DA is not a developmental toxin.

Reference: Morseth, S. L. (1987) Unpublished report number HLA 349-265 entitled "Rat Teratology Study with BPA-DA, BPA-BI and NMP" dated March 5, 1987 for General Electric Company, Plastics Business Operations, Pittsfield, MA, USA; from Hazleton Laboratories America, Inc., Vienna, VA, USA; and
Burdock, G.A. (1985). Unpublished report number 349-326 entitled "Pilot Rat Teratology Study: NMP, BPA-BI, BPA-DA, and a Positive Control" dated August October 29, 1985 for General Electric Company, Pittsfield, MA, USA; from Hazleton Laboratories America, Inc., Vienna, VA, USA.

Reliability: (Klimisch Code 1) Reliable without restrictions.